Remarks

Claims 1-62 and 68-75 are pending. Claims 1 and 53 have been amended to more clearly claim what the applicants consider to be their invention. New claims 76-81 have been added.

Claim 1 was amended to recite wherein the capture tag is not a nucleic acid. This amendment finds support at least on page 36, line 19 – page 38, line 16.

Claim 53 was amended to recite that the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody. This finds support at least on page 36, lines 26-30.

New claim 77 recites that the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody. This finds support at least on page 36, lines 26-30.

New claims 76, 78 and 80 recite that the capture tag is a hapten, an antibody or an anti-antibody. This finds support at least on page 36, lines 26-30.

New claim 79 recites that the capture tag is not a nucleic acid. This finds support at least on page 36, line 19 – page 38, line 16.

Support for new claim 81 can be found at least in original claim 1 on which the language of claim 81 is based. New claim 81 also recites that the capture tag, wherein the capture tag is a hapten, an antibody, or an anti-antibody. This finds support at least on page 36, lines 26-30.

Summary of Interview

Applicant would like to thank the Examiner and her Supervisor for their comments during the interview of October 12, 2005.

Regarding the obviousness rejection of the claims, the Supervisor indicated the Patent Office's position (that Lizardi '229 teaches a capture tag that is an antibody and that a nucleotide to nucleotide interaction between the primer and target DNA molecule as taught in Lizardi '229 meets the generic limitation of a nucleotide as a capture tag) is based on the broad definition of a "ligand" as a capture tag in the present application.

Also, regarding the obviousness rejection of the claims, the Supervisor indicated the Patent Office's position on Applicants' *In re Ratti* argument (that the combination of the '229 patent and the '024 patent would not render the method of the '229 patent inoperable). The Supervisor further added that if "ligand" was removed from the claim language, he believes the argument would be plausible. Applicants noted that they never argued that the combination of

the '229 patent and the '024 patent would not render the method of the '229 patent inoperable, but rather they argued that the Examiner's proposed modification of the '229 method with the method of the '024 patent would alter the fundamental principle of operation of the '229 method, which Applicant's maintain is the proper legal standard for overcoming an obviousness rejection on this basis.

Also, regarding the obviousness rejection of the claims, the Supervisor indicated the Patent Office's position on claims 48 and 53, which do not limit the capture tags to haptens, ligands, ligand binding molecules, and antibodies or anti-antibodies (that the general concept of the use of nucleic acid capture tags in these modes is suggested by the method of the '229 patent). Applicants acknowledged that the claims do not limit the capture tags as described above, however, Applicants pointed out that the method in the '229 patent does not disclose or suggest adding capture tags to cDNA nor the use of RT primers having capture tags.

Applicants also indicated that there is no disclosure in the '229 patent of where the association between the rolling circle replication primers and the cDNA occurs via the capture tag.

Rejections Under 35 U.S.C. § 103

1. Claims 1-29, 31-47, 53-58, 61, 62, 68, and 70-72 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi et al. (U.S. Pat. No. 6,316,229 B1; Lizardi '229) in view of Lizardi (U.S. 2003/0032024 A1; Lizardi '024). Applicants respectfully traverse this rejection.

In order for a reference or a combination of references to make obvious a claim or claims, "[f]irst, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2143.

Lizardi '229 discloses compositions and a method for detecting single nucleic acid molecules using rolling circle amplification (RCA) of amplification target circles (ATC), primed by immobilized primers. In one form of the method, referred to as bipartite primer rolling circle

amplification (BP-RCA), RCA of the ATC depends on the formation of a primer by target-mediated ligation. In BP-RCA a probe and a combination probe/primer oligonucleotide can hybridize to adjacent sites on a target sequence in the presence of a nucleic acid molecule having the target sequence, thus allowing the probes to be ligated together. The ligated primer can then be used to prime replication of its cognate ATC. Lizardi '229 fails to disclose or suggest use of a capture tag to associate cDNA with a rolling circle replication primer where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid. The passages of Lizardi '229 cited in the Office Action also fail to disclose or refer specifically to RT primers. The passages of Lizardi '229 cited in the Office Action mailed May 23, 2005 (herein referred to as the "Office Action") also fail to disclose RT primers that comprise a capture tag or use of such a capture tag to associate a rolling circle replication primer with cDNA. The passages of Lizardi '229 cited in the Office Action also fail to disclose RT primers that comprise a rolling circle replication primer portion or use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. Furthermore, the passages of Lizardi '229 cited in the Office Action fail to provide any suggestion or motivation to use anything other than the two oligonucleotides (the half probe and a probe/primer) in the disclosed bipartite primer rolling circle amplification (BP-RCA) reaction.

Lizardi '024 discloses compositions and methods for amplifying nucleic acid sequences based on the presence of a specific target sequence or analyte. In one form of the method, referred to as ligation-mediated rolling circle amplification (LM-RCA), RCA of the ATC depends on the hybridization of an open circle probe (OCP) to the target sequence, followed by ligation of the ends of the OCP to form an ATC. Lizardi '024 further describes a nucleic acid tag coupled to a specific binding molecule. The passages of Lizardi '024 cited in the Office Action and in the Advisory Action fail to explain how such a composition relates to the method of Lizardi '229. Not only does Lizardi '024 fail to suggest a modification of Lizardi '229 to use an antibody rather than nucleic acid hybridization to associate the half probe or probe/primer of Lizardi '229 with a target DNA, the Office Action and the Advisory Action completely fail to address this distinction between Lizardi '229 and the claimed method. Furthermore, the passages

of Lizardi '024 cited in the Office Action and in the Advisory Action fail to disclose or refer specifically to RT primers. The passages of Lizardi '024 cited in the Office Action and in the Advisory Action also fail to disclose RT primers that comprise a capture tag or use of such a capture tag to associate a rolling circle replication primer with cDNA. The passages of Lizardi '024 cited in the Office Action and in the Advisory Action also fail to disclose RT primers that comprise a rolling circle replication primer portion or use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle.

(a) Arguments For Claims 1-17, 18-29, 31-47, 56-58, 61, 68 and 71

(i) In the method of claims 1-17, 18-29, 31-47, 56-58, 61, 68 and 71, cDNA produced from mRNA is associated with rolling circle replication primers, where the rolling circle replication primers (claims 1-29, 31-47, and 68) or the cDNA (claims 56-58, 61, and 71) comprise a capture tag, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, where the capture tag is not a nucleic acid, and where the association between the rolling circle replication primer and cDNA occurs via the capture tag. That is, the claims require that either the rolling circle replication primer comprises a capture tag or the cDNA comprises a capture tag and that the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody and not a nucleic acid. The claims further require that the association between the rolling circle replication primers and cDNA occurs via the capture tag (see step (c) of claim 1; step (c) of claim 56, lines 6-8 of claim 68; and lines 6-8 of claim 71).

The Office Action alleges (page 2, line 25 – page 3, line 2) that Lizardi '229 teaches "mixing one or more rolling circle replication primers with the cDNA strands under conditions that promote association of the cDNA strands with the rolling circle replication primers, wherein the rolling circle replication primers each comprise a capture tag, and wherein association occurs via the capture tag." For support, the Office Action cites column 42, lines 27-52 of Lizardi '229, which describes formation of a rolling circle replication primer by target-mediated ligation of two oligonucleotides: a half probe and a probe/primer. In the cited passage of Lizardi '229 the half probe and a portion of the probe/primer hybridize to a target DNA molecule via base

pairing. Thus, association of the primer and the target DNA molecule in Lizardi '229 occurs by a nucleotide to nucleotide base pairing interaction between the sequences of the target DNA molecule and of the half probe and probe/primer. As in the currently amended form of the claims, the capture tag is not a nucleic acid. As such, the nucleotide to nucleotide base pairing interaction between the sequences of the target DNA molecule and of the half probe and probe/primer does not meet the current claim requirements of a capture tag.

Lizardi '024 was cited for allegedly disclosing a capture tag that is an antibody. The Office Action cites paragraph 0019, lines 19-22 of Lizardi '024 which describes using a nucleic acid tag coupled to a specific binding molecule. The Office Action fails to explain how such a composition relates to either Lizardi '229 or the claimed use of capture tags. Nothing in Lizardi '024 suggests modification of Lizardi '229 to use an antibody rather than nucleic acid hybridization to associate the half probe or probe/primer of Lizardi '229 with a target DNA. The Office Action completely fails to address this distinction between Lizardi '229 and the claimed method. Mere existence and use of an antibody in Lizardi '024 does not constitute any disclosure or suggestion of the use of an antibody capture tag as presently claimed. There is simply no suggestion of any connection between the hybridization of probes to DNA of Lizardi '229 and any use of the nucleic acid tag/specific binding molecule of Lizardi '024.

The Advisory Action alleges that it would be obvious to substitute an antibody for the nucleotide tag because it would improve specificity and enhance target discrimination. While use of an antibody as a capture tag might be possible, this does not satisfy the Examiner's burden of providing evidence of a teaching, motivation or suggestion present in either the '229 or '024 reference to substitute the '024 antibody for the half probe or the probe/primer used in the '229 method.

The cited prior art must provide a description of every element of the claimed method and provide a suggestion or motivation to combine the prior art to arrive at the claimed method. The cited publications both fail to disclose every element of the claimed method (use of a capture tag for association of a rolling circle replication primer with cDNA, wherein the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid, for example) and any suggestion or motivation to combine such

(non-existent) elements to arrive at the claimed method. As it stands, the present rejection merely refers to irrelevant aspects of both Lizardi '229 and Lizardi '024 and states without support that Lizardi '229 teaches "mixing one or more rolling circle replication primers with the cDNA strands under conditions that promote association of the cDNA strands with the rolling circle replication primers, wherein the rolling circle replication primers each comprise a capture tag, and wherein association occurs via the capture tag," and that Lizardi '024 "teaches the capture tag is an antibody." No rationale for combination of these disparate elements is provided and none is apparent. Applicants note in particular that it has not been established, nor is it apparent, how or why one of skill in the art would think that the nucleic acid tag/specific binding molecule of Lizardi '024 could or should be used in the BP-RCA method of Lizardi '229. This does not meet the burden of the Patent Office to establish a prima facie case of obviousness. For at least these additional reasons, claims 1-17, 18-29, 31-47, 56-58, 61, 68 and 71 are not obvious in view of the cited publications.

Because the rejection clearly fails to provide any evidence, reasoning or rationale that could possibly support the present rejection, and because such failure constitutes a failure to establish a prima facie case of obviousness, Applicants note that the present rejection must either be withdrawn or, if the rejection is supplemented in the next Office Action, finality cannot be maintained. Again, Applicants emphasize that the flaws in the present rejection mandate that the claims cannot remain under final rejection or remain under rejection on the present evidence.

(ii) A rejection under 35 U.S.C. 103 cannot be sustained if the proposed modification would alter the fundamental principle of operation of the prior art to be modified. *In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349(CCPA 1959).

The Advisory Action alleges that it would be obvious to combine the nucleic acid tag coupled to a specific binding molecule of Lizardi '024 with the method of Lizardi '229. In other words, the Advisory Action alleges that one of skill in the art would be motivated to substitute a nucleic acid tag coupled to a specific binding molecule for one or both of the oligonucleotides of Lizardi '229. Applicants respectfully submit that, not only do the passages of Lizardi '229 and Lizardi '024 cited in the Office Action fail to explain the compositions of Lizardi '024 relates to the method of Lizardi '229 (see above), the modification of the method of Lizardi '299 cited in

the rejection as suggested in the rejection would alter the fundamental principle of operation of the method and thus for at least this reason the present rejection cannot be sustained.

As described above, Lizardi '024 was cited for allegedly disclosing a capture tag that is an antibody. The Advisory Action cites paragraph 0019, lines 19-22 of Lizardi '024 which describes using a nucleic acid tag coupled to a specific binding molecule. Lizardi '229 discloses a method of carrying out bipartite primer rolling circle amplification (BP-RCA) where rolling circle amplification (RCA) of the amplification target circle (ATC) depends on the formation of a primer by target mediated ligation (see column 41, lines 5-8). The method disclosed by Lizardi '229 requires formation of a rolling circle replication primer by target-mediated ligation of two oligonucleotides: a half probe and a probe/primer. The half probe and a portion of the probe/primer are engineered such that they will hybridize to a target DNA molecule via base pairing. Thus, association of the primer and the target DNA molecule in Lizardi '229 occurs by a nucleotide to nucleotide base pairing interaction between the sequences of the target DNA molecule and the half probe and probe/primer, not by interaction of, for example, a hapten or ligand. As indicated above and in the amended claim 1, the capture tag is not a nucleic acid, as such, such an interaction fails to meet the requirements of a capture tag. In fact, the nucleotide to nucleotide interaction is required for the method of Lizardi '229 to function properly (see Lizardi '229 Column 4, lines 15-18 describing that if the nucleotide to nucleotide interaction between the primer and the target DNA molecule does not occur, the ATC used in the BP-RCA method, will not attach to the primers). In other words, for the method of BP-RCA to function properly, formation of a primer by target-mediated ligation of a probe and a combination probe-primer oligonucleotide that can hybridize to adjacent sites on the target sequence allowing the probe and probe-primer to be ligated together must occur (see Lizardi '229 Column 4, lines 4-11). Only those ATCs complementary to ligated primers will be amplified (see column 4, lines 29-30).

Even if, for the sake of argument, an antibody was used to bind the half/probe or probe/primer of Lizardi '229 to the target DNA of Lizardi '229, this would defeat the purpose, and be contrary to the fundamental principles, of Lizardi '229 in having the formation of a

rolling circle replication primer be formed by target-mediated nucleic acid base pairing and ligation of two oligonucleotides. Lizardi '299 specifically states that:

> "In one form of the method, referred to as bipartite primer rolling circle amplification (BP-RCA), RCA of the amplification target circle (ATC) depends on the formation of a primer by target-mediated ligation. In the presence of a nucleic acid molecule having the target sequence, a probe and a combination probe/primer oligonucleotide can hybridize to adjacent sites on the target sequence allowing the probes to be ligated together. By attaching the first probe to a substrate such as a bead or glass slide, unligated probe/primer can be removed after ligation. The only primers remaining will be primers ligated, via the probe portion of the probe/primer, to the first probe. The ligated primer can then be used to prime replication of its cognate ATC. In this way, an ATC will only be replicated if the target sequence (to which its cognate probe/primer is complementary) is present.

Column 4, lines 4-18 (emphasis added).

The Advisory Action alleges that the combination of the '024 patent with the '229 patent would simply change the operation of the methods disclosed in the '229 patent. Applicants submit that not only would the combination of the '024 patent with the '229 patent change the operation of the methods disclosed in the '229 patent, such a change, as required by the logic of the present rejection, would alter the fundamental principle of operation of the method of Lizardi '229. Even if the Lizardi '229 or Lizardi '024 did suggest modification, which Applicants submit is not the case, of the method of Lizardi '229 using the nucleic acid tag coupled to a specific binding molecule of Lizardi '024, use of an antibody to associate the probe or probe/primer to the target DNA of Lizardi '229 would prevent ligation and hybridization-based sequence discrimination of the formation of primers in the method of Lizardi '229. Such a change would render the method of Lizardi '229 entirely inoperable.

Applicants submit that it cannot be contested that rendering a method inoperable would clearly alter the fundamental principle of operation of a method. Such a change in the principle of operation of the method of Lizardi '299, which results from the modification proposed by the rejection, renders the rejection unsustainable. Accordingly, for at least these additional reasons, Lizardi '299 and Lizardi '024 fail to make claims 1-17, 18-29, 31-47, 56-58, 61, 68 and 71

obvious variations of claims 1-72 of Lizardi '299. As such, Applicants respectfully request withdrawal of this rejection.

B. Arguments For Claims 53-55 and 70

In the method of claims 53-55 and 70, cDNA produced from mRNA is associated with rolling circle replication primers, where the RT primers used to produce the cDNA comprise capture tags, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. That is, the claims require use of an RT primer that comprises a capture tag that is the basis for the association of the rolling circle replication primers and the cDNA.

The cited passage of Lizardi '229 fails to disclose or refer specifically to RT primers, fails to disclose RT primers that comprise a capture tag, and fails to disclose use of such a capture tag to associate a rolling circle replication primer with cDNA. The Office Action mailed May 23, 2005 alleged (page 2, lines 19-22) that Lizardi '229 teaches "mixing one or more RT primers with a nucleic acid sample and reverse transcribing to produce cDNA strands each comprising one of the RT primers, wherein each RT primer comprises a reverse transcription primer portion." For support, the Office Action cited column 77, line 2 of Lizardi '229, which merely mentions use of cDNA produced by reverse transcription. Applicants maintain that the passage does not mention any primers used to produce cDNA, does not describe any features of such primers, and does not describe the use of such primers. Thus, the cited passage of Lizardi '229 fails to disclose or refer specifically to RT primers, fails to disclose RT primer that comprise a capture tag, and fails to disclose use of such a capture tag to associate a rolling circle replication primer with cDNA.

The Advisory Action attempted to circumvent the lack of such a disclosure by alleging that Lizardi '229 teaches that RNA can be used with the methods disclosed therein and that Lizardi '229 teaches cDNA which inherently requires the use of RT primers (see Advisory Action page 2, lines 22-24). The Advisory Action further alleges that a practitioner of ordinary skill in the art recognizes the need for using RT primers when working with RNA and moreover, primers are primers (see Advisory Action page 2, lines 23-24). The Advisory Action then makes the leap that because the combination of the '229 and '024 patents allegedly render the instant

invention obvious with respect to DNA primers then it necessarily renders the instant invention obvious with respect to RT primers (see Advisory Action page 2, lines 25-27).

First, Applicants respectfully submit that primers are not always just primers. The currently claimed RT primers are not "just" primers. The currently claimed RT primers comprise special components, capture tags, that "all" primers do not just have. Although, it may be true that general RT primers and DNA primers are generally similar, the currently claimed RT primers are not simply primers. Even assuming for the sake of argument that RT primers are inherent in Lizardi '229, the Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise capture tags wherein the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid, and that the association between the rolling circle replication primers and cDNA occurs via the capture tags.

Lizardi '024 fails to supplement the elements missing from Lizardi '229. Lizardi '024 was cited for allegedly disclosing that a "capture tag" can be an antibody as well as allegedly disclosing mixing one or more half probes with the cDNA strands where each half probe is designed to hybridize to a cDNA strand adjacent to where a capture probe hybridizes, ligating the half probes and capture probes, and after ligation, incubating the capture probes at a temperature above the melting temperature of the capture probe but below the melting temperature of the ligated capture probe/half probe. However, Lizardi '024, like Lizardi '229, fails to disclose RT primers that comprise a capture tag wherein the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid. The Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise a capture tag wherein the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and wherein the capture tag is not a nucleic acid and that the association between the rolling circle replication primers and cDNA occurs via the capture tags.

Lizardi '229 and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claims 53-55 and 70. Accordingly, and for all of the above reasons,

Lizardi '229 and Lizardi '024 fail to make obvious claims 53-55 and 70. Applicants respectfully request withdrawal of this rejection.

C. Arguments for Claims 62 and 72

The method of claims 62 and 72 requires the use of RT primers that comprise a rolling circle replication primer portion and use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. That is, the claims require use of an RT primer that comprises a rolling circle replication primer portion that is the basis for the association of the rolling circle replication primers with amplification target circles.

The cited passage of Lizardi '229 fails to disclose RT primers that comprise a rolling circle replication primer portion or use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. The Office Action alleges (page 2, lines 19-21) that Lizardi '229 teaches "mixing one or more RT primers with a nucleic acid sample and reverse transcribing to produce cDNA strands each comprising one of the RT primers, wherein each RT primer comprises a reverse transcription primer portion." For support, the Office Action cites column 77, line 2 of Lizardi '229, which merely mentions use of cDNA produced by reverse transcription. The passage does not mention any primers used to produce cDNA, does not describe any features of such primers, and does not describe the use of such primers. Thus, the cited passage of Lizardi '229 fails to disclose or refer specifically to RT primers, fails to disclose RT primers that comprise a rolling circle replication primer portion, and fails to disclose use of such an RT primer to associate the rolling circle replication primer portion with an amplification target circle.

The Office Action attempts to circumvent the lack of such a disclosure by alleging that Lizardi '229 teaches that RNA can be used with the methods disclosed therein and that Lizardi '229 teaches cDNA which inherently requires the use of RT primers (see Office Action page 10, line 23 – page 11, line 1). Even assuming RT primers inherent in Lizardi '229, the Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise rolling circle replication primer portions and that the RT primers associate with amplification target circles via the rolling circle replication primer portions.

Lizardi '024 fails to supplement the elements missing from Lizardi '229. Lizardi '024 was cited for allegedly disclosing that a "capture tag" can be an antibody as well as allegedly disclosing mixing one or more half probes with the cDNA strands where each half probe is designed to hybridize to a cDNA strand adjacent to where a capture probe hybridizes, ligating the half probes and capture probes, and after ligation, incubating the capture probes at a temperature above the melting temperature of the capture probe but below the melting temperature of the ligated capture probe/half probe. However, Lizardi '024 fails to disclose RT primers that comprise a rolling circle replication primer portion, and fail to disclose use of such an RT primer to associate the rolling circle replication primer portion with an amplification target circle. The Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise rolling circle replication primer portions and that the RT primers associate with amplification target circles via the rolling circle replication primer portions.

The Advisory Action again attempts to circumvent the lack of such a disclosure by alleging that Lizardi '229 teaches that RNA can be used with the methods disclosed therein and that Lizardi '229 teaches cDNA which inherently requires the use of RT primers (see Advisory Action page 2, lines 22-24). The Advisory Action further alleges that a practitioner of ordinary skill in the art recognizes the need for using RT primers when working with RNA and moreover, primers are primers (see Advisory Action page 2, lines 23-24). The Advisory Action then makes the leap that because the combination of the '229 and '024 patents render the instant invention obvious with respect to DNA primers then it necessarily renders the instant invention obvious with respect to RT primers. (see Advisory Action page 2, lines 25-27).

Again, Applicants respectfully submit that primers are not always just primers. The currently claimed RT primers are not "just" primers. The currently claimed RT primers comprise a rolling circle replication primer portion and use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle. Although, it may be true that general RT primers and DNA primers are generally similar, the currently claimed RT primers are not simply primers. The claimed RT primers are specifically designed to contain sequences that serve as a basis for association with a

specific ATC. Even assuming for the sake of argument that RT primers are inherent in Lizardi '229, the Advisory Action as well as the Office Action completely fail to address the requirement of the claims that the RT primers used to produce the cDNA comprise a rolling circle replication primer portion and use of such a rolling circle replication primer portion of an RT primer to associate the rolling circle replication primer portion with an amplification target circle.

Lizardi '229 and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claims 62 and 72. Accordingly, and for all of the above reasons, Lizardi '229 and Lizardi '024 fail to make obvious claims 62 and 72. Applicants respectfully request withdrawal of this rejection.

D. Additional Arguments for Claims 37-39

The method of claims 37-39 also requires the use of RT primers that comprise a capture tag. The cited passage of Lizardi '229 fails to disclose or refer to RT primers that comprise a capture tag. The Office Action alleges (page 6, lines 9-12) that Lizardi '229 teaches "the RT primer comprises a capture tag" and that "the capture tag is selected from the group consisting of biotin, digoxigenin, bromodeoxyuridine, or other hapten." For support, the Office Action cites column 23, lines 50-67 of Lizardi '229, which discloses detection labels for nucleic acid amplified using rolling circle amplification and rolling circle transcription (see column 23, lines 18-23). The labels disclosed in the cited passage of Lizardi '229 are to be incorporated into or associated with amplified nucleic acids. This is not the same as what is presently claimed.

The method of claims 37-39 requires the use of RT primers that comprise a capture tag. Furthermore, the present method uses the claimed RT primers to produce cDNA the presence of which allows production of amplified nucleic acid. In other words, neither the claimed RT primers nor the claimed cDNA produced with the RT primers are equivalent to the amplified nucleic acid referred to in column 23 of Lizardi '229. Furthermore, Lizardi '229 fails to disclose RT primers and cDNA that comprise the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens).

Lizardi '024 fails to supplement the elements missing from Lizardi '229. Lizardi '024 was cited for allegedly disclosing that a "capture tag" can be an antibody as well as allegedly disclosing mixing one or more half probes with the cDNA strands where each half probe is

designed to hybridize to a cDNA strand adjacent to where a capture probe hybridizes, ligating the half probes and capture probes, and after ligation, incubating the capture probes at a temperature above the melting temperature of the capture probe but below the melting temperature of the ligated capture probe/half probe. However, Lizardi '024 fails to disclose or refer to RT primers and fails to disclose RT primers and cDNA that comprise the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens).

Once again, the Advisory Action again attempts to circumvent the lack of such a disclosure by alleging that Lizardi '229 teaches that RNA can be used with the methods disclosed therein and that Lizardi '229 teaches cDNA which inherently requires the use of RT primers (see Advisory Action page 2, lines 22-24). The Advisory Action further alleges that a practitioner of ordinary skill in the art recognizes the need for using RT primers when working with RNA and moreover, primers are primers (see Advisory Action page 2, lines 23-24). The Advisory Action then makes the leap that because the combination of the '229 and '024 patents render the instant invention obvious with respect to DNA primers then it necessarily renders the instant invention obvious with respect to RT primers (see Advisory Action page 2, lines 25-27).

Applicants again respectfully submit that primers are not always just primers. The currently claimed RT primers are not "just" primers. The currently claimed RT primers comprise special components, capture tags, that "all" primers do not just have. Although, it may be true that general RT primers and DNA primers are generally similar, the currently claimed RT primers are not simply primers. In addition, the currently claimed RT primers comprise a capture tag that comprises labels such as biotin, digoxigenin, bromodeoxyuridine, and other haptens. Even assuming RT primers are inherent in Lizardi '229, the Office Action completely fails to address the requirement of the claims that the RT primers used to produce the cDNA comprise capture tags in general, much less RT primers that specifically comprise a capture tag that comprises labels such as biotin, digoxigenin, bromodeoxyuridine, and other haptens.

Thus, Lizardi '229 and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claims 37-39. Accordingly, Lizardi '229 and Lizardi '024 do not make obvious claims 37-39. Applicants therefore respectfully requests withdrawal of this rejection.

E. Additional Arguments for Claims 39-41

The method of claims 39-41 also requires the use of cDNA that comprises a capture tag. The cited passage of Lizardi '229 fails to disclose cDNA that comprises a capture tag. The Office Action alleged (page 6, lines 13-18) that Lizardi '229 teaches "the cDNA strands comprise capture tags" and that "the capture tags on the cDNA strands are selected from the group consisting of biotin, digoxigenin, bromodeoxyuridine, or other hapten." For support, the Office Action cited column 23, lines 50-67 of Lizardi '229, which discloses detection labels for nucleic acid amplified using rolling circle amplification and rolling circle transcription (see column 23, lines 18-23). The labels disclosed in the cited passage of Lizardi '229 are to be incorporated into or associated with amplified nucleic acids, not with the cDNA produced from RNA. This is not the same as what is presently claimed.

The Advisory Action attempts to circumvent the lack of disclosure by citing Example 4 of Lizardi '229. Applicants respectfully submit that Example 4 of Lizardi '229 likewise fails to disclose or refer to cDNA comprising a capture tag and fails to disclose or refer to cDNA that comprises the listed labels such as biotin, digoxigenin, bromodeoxyuridine, and other haptens. Example 4 describes detection of human mRNA containing a mutant form of ornithine transcarbamylase (OTC) using cDNA generated by reverse transcriptase (see Lizardi '299 Column 76, line 63- Column 77, line 2). The method utilizes a reverse transcriptase reaction to generate cDNA (see Lizardi '299 Column 77, lines 6-20). Nowhere, in the reverse transcription reaction are RT primers that comprise a capture tag used, nor do the resulting cDNA molecules comprise a capture tag of any sort. The next step in the reaction is to incubate the cDNA molecules with OCPs and Gap probes to perform LM-RCA. Then, the TS-DNA produced in the LM-RCA reaction serve as the template in a reverse transcription reaction, where biotinylated RNA is produced. The biotin incorporated in the RNA then serves as a means to attach the RNA to a glass slide, not as a means of associating a rolling circle replication primer with the RNA. While it is true that the RNA produced in Example 4 is biotinylated, the resulting RNA is not the same as the cDNA comprising a capture tag of the claimed method.

The present method uses the presence of cDNA to enable production of amplified nucleic acid. In other words, the claimed cDNA is not equivalent to the amplified nucleic acid referred

to in column 23 of Lizardi '229 nor is it the equivalent to the RNA produced in Example 4 of Lizardi '229. The cDNA of the claimed method serves as the template to which the rolling circle replication primer associates, wherein the association occurs via the capture tag. The general assertion made in the Advisory Action, that Lizardi '229 discloses RNA and further discloses cDNA fails to account for these differences. Lizardi '229 fails to disclose or refer to cDNA that comprises the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens).

Lizardi '024 fails to supplement the elements missing from Lizardi '229. Lizardi '024 was cited for allegedly disclosing that a "capture tag" can be an antibody as well as allegedly disclosing mixing one or more half probes with the cDNA strands where each half probe is designed to hybridize to a cDNA strand adjacent to where a capture probe hybridizes, ligating the half probes and capture probes, and after ligation, incubating the capture probes at a temperature above the melting temperature of the capture probe but below the melting temperature of the ligated capture probe/half probe. However, Lizardi '024 fails to disclose or refer to cDNA and fails to disclose or refer to cDNA that comprises the listed labels (such as biotin, digoxigenin, bromodeoxyuridine, and other haptens).

Thus, Lizardi '229 and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claims 39-41. Accordingly, Lizardi '229 and Lizardi '024 do not make obvious claims 39-41. Applicants therefore respectfully request withdrawal of this rejection.

F. Additional Arguments for Claims 46 and 47

The method of claims 46 and 47 also requires the use of cDNA that comprises a capture tag. The cited passage of Lizardi '229 fails to disclose cDNA that comprises a capture tag. The Office Action alleged (page 7, lines 1-2) that Lizardi '229 teaches "the capture tags on the cDNA strands are biotin." For support, the Office Action cited column 53, lines 53-57 of Lizardi '229, which discloses labels in tandem sequence DNA (TS-DNA; which is the product of rolling circle amplification). The labels disclosed in the cited passage of Lizardi '229 are to be incorporated into or associated with amplified nucleic acids (TS-DNA). This is not the same as what is presently claimed.

The present method uses the presence of cDNA to enable production of amplified nucleic acid. In other words, the claimed cDNA is not equivalent to the amplified nucleic acid (TS-DNA) referred to in column 53 of Lizardi '229. Lizardi '229 fails to disclose or refer to cDNA and fails to disclose cDNA that comprises biotin.

Lizardi '024 fails to supplement the elements missing from Lizardi '229. Lizardi '024 was cited for allegedly disclosing that a "capture tag" can be an antibody as well as allegedly disclosing mixing one or more half probes with the cDNA strands where each half probe is designed to hybridize to a cDNA strand adjacent to where a capture probe hybridizes, ligating the half probes and capture probes, and after ligation, incubating the capture probes at a temperature above the melting temperature of the capture probe but below the melting temperature of the ligated capture probe/half probe. However, Lizardi '024 fails to disclose or refer to cDNA and fails to disclose cDNA that comprises biotin.

The Advisory Action attempts to circumvent the lack of disclosure by relying again on Example 4 of Lizardi '229. Applicants respectfully submit that Example 4 of Lizardi '229 likewise fails to disclose or refer to cDNA comprising a capture tag and fails to disclose or refer to capture tags that comprises biotin or capture tags that comprise antibodies that bind biotin. Example 4 describes detection of human mRNA containing a mutant form of ornithine transcarbamylase (OTC) using cDNA generated by reverse transcriptase. (See Lizardi '299 Column 76, line 63- Column 77, line 2). The method utilizes a reverse transcriptase reaction to generate cDNA. (See Lizardi '299 Column 77, lines 6-20). Nowhere, in the reverse transcription reaction are RT primers that comprise a capture tag used, nor do the resulting cDNA molecules comprise a capture tag of any sort. The next step in the reaction is to incubate the cDNA molecules with OCPs and Gap probes to perform LM-RCA. Then, the TS-DNA produced in the LM-RCA reaction serve as the template in a reverse transcription reaction, where biotinylated RNA is produced. The biotin incorporated in the RNA then serves as a means to attach the RNA to a glass slide, not as a means of associating a rolling circle replication primer with the RNA. While it is true that the RNA produced in Example 4 is biotinylated, the resulting RNA is not the same as the cDNA or rolling circle replication primers comprising a capture tag of the claimed method.

The present method uses the presence of cDNA to enable production of amplified nucleic acid. In other words, the claimed cDNA is not equivalent to the amplified nucleic acid referred to in column 23 of Lizardi '229 nor is it the equivalent to the RNA produced in Example 4 of Lizardi '229. The cDNA of the claimed method serves as the template to which the rolling circle replication primer associates, wherein the association occurs via the capture tag. In claims 46 and 47, the cDNA comprises a capture tag of biotin and a rolling circle replication primer comprising a capture tag that is an antibody that binds biotin, respectfully. The general assertion made in the Advisory Action, that Lizardi '229 discloses RNA and further discloses cDNA fails to account for these differences. Lizardi '229 fails to disclose or refer to cDNA with a capture tag, fails to disclose or refer to cDNA that comprises biotin and fails to refer to a rolling circle replication primer that comprises and antibody that binds biotin.

Thus, Lizardi '229 and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claims 39-41. Accordingly, Lizardi '229 and Lizardi '024 do not make obvious claims 39-41. Applicants therefore respectfully request withdrawal of this rejection.

For all of the above reasons, Lizardi '229 and Lizardi '024 fail to make obvious claims 1-17, 18-29, 31-47, 53-58, 61, 62, 68, and 70-72.

2. Claim 30 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) in view of Lizardi '024 (US 2003/0032024) and in further view of Waggoner et al. (U.S. Pat. No. 6,008,373). Applicants respectfully traverse this rejection.

Applicants note that claim 30 depends from claim 1 and thus includes all of the limitations of claim 1. Applicants also note that the rejection applies Lizardi '229 and Lizardi '024 in the same way and for the same disclosures for which Lizardi '229 and Lizardi '024 were applied in the rejection of claims 1-17, 18-29, 31-47, 53-58, 61, 62, 68, and 70-72 under 35 U.S.C. § 103(a) addressed above. For at least the reasons discussed above, Lizardi '229 and Lizardi '024, either alone or in combination, fail to disclose or suggest each and every element of claim 1. Specifically, Lizardi '229 and Lizardi '024 either alone or in combination, fail to disclose or suggest rolling circle replication primers comprising capture tags, where the capture

tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags, and wherein the capture tag is not a nucleic acid.

Waggoner et al. fails to supplement the elements missing from Lizardi '229 and Lizardi '229. Waggoner et al. was cited for its disclosure of using phycoerythrin as a fluorophore in the detection label on an antibody. Waggoner et al. fails to disclose or suggest rolling circle replication primers comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags. Thus, Lizardi '229, Lizardi '024, and Waggoner et al., either alone or in combination, fail to disclose or suggest each and every element of claim 30. Accordingly, Lizardi '229, Lizardi '024, and Waggoner et al. do not make obvious claim 30. Applicants respectfully request withdrawal of this rejection.

3. Claims 48-52, 69 and 73 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) in view of Lizardi '024 (US 2003/0032024) and in further view of Cao et al. (U.S. 2002/0120409). Applicants respectfully traverse this rejection.

A. Arguments For Claims 48-52, and 69

With regard to claims 48-52, and 69 the Advisory Action applies Lizardi '229 and Lizardi '024 in the same way and for the same disclosures for which Lizardi '229 and Lizardi '024 were applied in the rejection of claims 1-17, 18-29, 31-47, 53-58, 61, 62, 68, and 70-72 under 35 U.S.C. § 103(a) addressed above. As noted in the Office Action (page 9, lines 10-11) Lizardi '229 and Lizardi '024 fail to teach fragmenting and labeling cDNA strands to form labeled fragmented cDNA. Applicants submit that Lizardi '229 and Lizardi '024 also fails to disclose or suggest adding a capture tag to the fragmented cDNA or associating a rolling circle replication primer with fragmented cDNA via a capture tag.

The cited passages of Cao et al. describe a method of fragmenting cDNA and incorporating a label into the cDNA, where the label can be biotin (see Cao et al. claim 1 and paragraphs 0045-0049). The incorporated label then serves as a means of detecting the labeled cDNA (see Cao et al., para. 49). Cao et al. does not disclose or suggest associating rolling circle

replication primers with the fragmented cDNA via the labels or any other component. Thus, the label of Cao et al. is not a capture tag as claimed.

Claims 48-52 involve a method of amplifying messenger RNA, involving fragmenting cDNA strands to form fragmented cDNA, adding a capture tag to the fragmented cDNA, mixing the fragmented cDNA with a set of capture probes under conditions that promote hybridization of the fragmented cDNA to the capture probes, mixing one or more rolling circle replication primers with the fragmented cDNA under conditions that promote association of the fragmented cDNA with the rolling circle replication primers, where the association occurs via the capture tag. Thus the claims require adding a capture tag to the fragmented cDNA where a rolling circle replication primer associates with the fragmented cDNA via the capture tag.

Claim 69 involves a method of using messenger RNA, the method comprising replicating one or more amplification target circles to produce one or more tandem sequence DNAs, where each tandem sequence DNA is coupled to a rolling circle replication primer, where the rolling circle replication primer is associated with a fragmented cDNA strand, where the fragmented cDNA strand is hybridized to a capture probe, where the fragmented cDNA comprises a capture tag, where the association of the rolling circle replication primer and the fragmented cDNA strand occurs via the capture tag. Thus, like claims 48-52, claim 69 requires that the fragmented cDNA comprises a capture tag where the rolling circle replication primer associates with the fragmented cDNA strand via the capture tag of the cDNA strand.

None of Lizardi '229, Lizardi '024 or Cao et al., either alone or in combination, disclose or suggest fragmented cDNA comprising a capture tag and association of a rolling circle replication primer with the fragmented cDNA via the capture tag. Therefore, the cited publications fail to disclose or suggest every limitation of the present claims. Accordingly, the cited publications fail to make obvious claims 48-52, and 69.

B. Arguments For Claim 73

With regard to claim 73, Applicants first note that claim 73 does not recite fragmented cDNA so it is not clear how the present rejection relates to claim 73. The Office Action applies Lizardi '229 and Lizardi '024 in the same way and for the same disclosures for which Lizardi '229 and Lizardi '024 were applied in the rejection of claims 1-17, 18-29, 31-47, 53-58, 61, 62,

68, and 70-72 under 35 U.S.C. § 103(a). As noted in the Office Action (page 9, lines 10-11) Lizardi '229 and Lizardi '024 fail to teach fragmenting and labeling cDNA strands to form labeled fragmented cDNA. Applicants submit that Lizardi '229 and Lizardi '024 also fail to disclose or suggest adding a capture tag to the fragmented cDNA, a rolling circle replication primer comprising a capture tag, or associating a rolling circle replication primer with fragmented cDNA via a capture tag.

The cited passages of Cao et al. describe a method of fragmenting cDNA and incorporating a label into the cDNA, where the label can be biotin. See Cao et al. claim 1 and paragraphs 0045-0049. The incorporated label then serves as a means of detecting the labeled cDNA (see Cao et al., para. 49). Cao et al. does not disclose or suggest associating rolling circle replication primers with the fragmented cDNA via the labels or any other component. Thus, the label of Cao et al. is not a capture tag as claimed. Cao et al. also fails to disclose or suggest a rolling circle replication primer comprising a capture tag, or associating a rolling circle replication primer with fragmented cDNA via a capture tag.

Claim 73 is a method of amplifying messenger RNA involving production of cDNA comprising capture tags, rolling circle replication primers comprising capture tags, and association of the cDNA and the rolling circle replication primers via the capture tags.

None of Lizardi '229, Lizardi '024 or Cao et al., either alone or in combination, discloses or suggests production of cDNA comprising capture tags, rolling circle replication primers comprising capture tags, and association of the cDNA and the rolling circle replication primers via the capture tags. First, none of the cited publications disclose or suggest associating a rolling circle replication primer with cDNA via a biotin capture tag in the cDNA. Second, the label of Cao et al. is not a capture tag as claimed. Third, Lizardi '229 and Lizardi '024 do not disclose or suggest cDNA comprising capture tags. Fourth, there is no nexus between the rolling circle amplification of Lizardi '229 or Lizardi '024 and the labeled cDNA of Cao et al., let alone any suggestion to modify the method of Lizardi '229 or Lizardi '024 to use the labeled cDNA of Cao et al. Thus, Lizardi '229, Lizardi '024 and Cao et al. fail to disclose or suggest every feature of claim 73 and fail to suggest combination of Lizardi '229, Lizardi '024, and Cao et al. to arrive at

the claimed method. Accordingly, Lizardi '229, Lizardi '024, and Cao et al. fail to make obvious claim 73.

For at least these reasons, Lizardi '229, Lizardi '024, and Cao et al. do not make obvious claims 48-52, 69 and 73. Applicants respectfully request withdrawal of this rejection.

4. Claims 59 and 60 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lizardi '229 (U.S. Pat. No. 6,316,229 B1) in view of Lizardi '024 (US 2003/0032024) and in further view of Shoemaker et al. (U.S. Pat. No. 6,713,257 B2). Applicants respectfully traverse this rejection.

Applicants note that claims 59 and 60 depend from claim 56 and thus include all the limitations of claim 56. Applicants also note that the rejection applies Lizardi '229 and Lizardi '024 in the same way and for the same disclosures for which Lizardi '229 and Lizardi '024 were applied in the rejection of claims 1-17, 18-29, 31-47, 53-58, 61, 62, 68, and 70-72 under 35 U.S.C. § 103(a) addressed above. For at least the reasons discussed above, Lizardi '229 and Lizardi '024 fail to disclose or suggest every limitation of claims 59 and 60. Specifically, Lizardi '229 and Lizardi '024, either alone or in combination, fail to disclose or suggest rolling circle replication primers comprising capture tags, where the capture tag is a hapten, a ligand, a ligand binding molecule, an antibody or an anti-antibody, and where the association between the rolling circle replication primers and cDNA occurs via the capture tags and wherein the capture tag is not a nucleic acid.

Shoemaker et al. fails to supplement the elements missing from Lizardi '229 and Lizardi '024. Shoemaker et al. was cited for its disclosure of using an amino-allyl dUTP in labeling cDNA. Shoemaker et al. fails to disclose or suggest the use of a capture tag to associate cDNA with a rolling circle replication primer. Thus, Lizardi '229, Lizardi '024, and Shoemaker et al., either alone or in combination, fail to disclose or suggest each and every element of claims 59 and 60. Accordingly, Lizardi '229, Lizardi '024 and Shoemaker et al. do not make obvious claims 59 and 60. Applicants respectfully request withdrawal of this rejection.

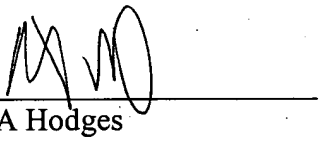
Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to

directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

A Credit Card Payment Form PTO-2038 authorizing payment in the amount of $935.00, representing $510.00 for the fee for a small entity under 37 C.F.R. § 1.17(a)(3), $250.00 for the fee for a small entity under 37 C.F.R. § 41.20(b)(1), $100.00 for the fee for a small entity under 37 C.F.R. § 1.16(h), and $75.00 for the fee for a small entity under 37 C.F.R. § 1.16(i), a Request for Extension of Time and a Notice of Appeal from the Primary Examiner to the Board of Patent Appeals and Interferences are enclosed. This amount is believed to be correct; however, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.



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